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### Authors

Kazemi, Abraham  
Cline, Abigail  
Cardwell, Leah A.  
et al.

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# Psoriasis therapy and aortic inflammation — translating statistical to clinical significance

Abrahem Kazemi<sup>1</sup> MD, Abigail Cline<sup>2</sup> MD PhD, Leah A. Cardwell<sup>3</sup> MD, Steven R. Feldman<sup>3,4,5</sup> MD PhD

Affiliations: <sup>1</sup>Howard University College of Medicine, Washington, DC, USA, <sup>2</sup>Augusta University Medical Center, Augusta, Georgia, USA, <sup>3</sup>Center for Dermatology Research, Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA, <sup>4</sup>Department of Pathology, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA, <sup>5</sup>Department of Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA

Corresponding Author: Abrahem Kazemi MD, 8159 Old Barrington Boulevard, Fairfax Station, VA 22039, Tel: 703-340-0289, Email: [kazemiabraham@gmail.com](mailto:kazemiabraham@gmail.com)

## Abstract

Psoriasis patients are known to have comorbid aortic vascular inflammation, which is one of the leading causes of cardiovascular morbidity and mortality in this population. Many studies report statistically significant improvements in aortic vascular inflammation after use of tumor necrosis factor inhibitors or interleukin-12/23 antagonists. However, the clinical significance in reduction of adverse cardiovascular events in psoriatic patients owing to biologic therapy has not been examined. Regardless of clinically significant cardiovascular benefits, dermatologists should continue to treat psoriasis patients optimally to mitigate the unfavorable effect this disease has on quality of life.

*Keywords: psoriasis, aortic vascular inflammation, biologic therapy, biologics, clinical significance, statistical significance*

## Introduction

Psoriasis is an independent risk factor for life-threatening cardiovascular mortality secondary to vascular inflammation [1-5]. Treatment with systemic biologic therapy such as adalimumab, etanercept, infliximab, and/or ustekinumab may improve both psoriasis and associated disease [1, 2, 4, 5], specifically aortic inflammation. Whether the reported statistically significant decrease in aortic inflammation by biologic therapy correlates with a clinically significant risk reduction in adverse cardiovascular events remains to be seen.

There is an increased prevalence of aortic inflammation in psoriatic patients [1, 3, 4]. Various circulating biomarkers such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-17 (IL-17) are elevated in psoriasis patients and accelerate comorbid aortic inflammation [3]. Owing to the shared pathophysiologic mechanisms driving psoriasis and vascular inflammation, patients may benefit from therapeutic inhibition and systemic reduction of these pro-inflammatory molecules. Anti-TNF agents and an anti-interleukin 12/23 agent significantly reduce aortic inflammation and psoriatic plaque burden [1, 2, 4, 5]. However, statistical significance achieved in these studies does not necessarily translate to clinically significant improvement in cardiovascular outcomes.

## Discussion

A cohort of 17 participants receiving anti-TNF therapy had reduced aortic inflammation to an extent comparable to that of low-dose statin therapy [1], (Table 1). Although statistically significant reductions in psoriasis severity and aortic inflammation were achieved in the treated group [1], anti-TNF therapy did not necessarily mitigate the risk or incidence of adverse cardiovascular events. Statistical analysis of a pilot study of 16 severely psoriatic adults on anti-TNF therapy did not demonstrate a clinically significant improvement in cardiovascular morbidity, mortality, or inflammation [2], (Table 1). An observational study investigated the relationship between aortic inflammation and

serum concentrations of the psoriatic biomarkers TNF and IL-6, and the neutrophil biomarker IL-17 [3], (Table 1). Although severe psoriasis plaques may promote aortic inflammation, causality and clinical significance were not assessed [3]. A feasibility study of 10 psoriasis patients receiving ustekinumab demonstrated a statistically significant decrease in aortic vascular inflammation [4], (Table 1). However, the study was not powered to assess whether the reduction in aortic inflammation reduced clinically meaningful cardiovascular events. Finally, although a prospective study of 28 patients with severe psoriasis demonstrated decreased CAD progression in the biologically-treated cohort [5], it did not test whether this reduced the risk of cardiovascular events (Table 1).

Although there is growing evidence that statistically significant improvements in measures of vascular inflammation can be achieved with treatments that

reduce inflammation in psoriasis, the clinical significance of these improvements is not yet well characterized. Whereas improvements in relative risk often sound impressive, absolute risk reduction (ARR) and number needed to treat (NNT) provide a clearer picture of clinically meaningful benefit. Such absolute measures of benefits associated with psoriasis treatment-induced vascular anti-inflammatory activity have not yet been clearly defined. If there is a risk reduction in adverse cardiovascular events related to biologic therapy in psoriasis, then that could be a valuable, clinically significant finding. However, until this association is ascertained, dermatologists should continue to treat psoriasis with the available most effective treatment options in view of the disease's vast detrimental effect on patients' quality of life, irrespective of whether these treatments also offer cardiovascular benefits.

Table 1. *Studies examined, and a summary of their results [1-5].*

Study	Study Design	Outcome Measures	Results	Comments/Limitations
Dey et al. (2017) [1] Country: USA	Prospective observation of case cohort of 115 psoriasis patients with low CV risk by FRS; 17 with severe psoriasis underwent anti-TNF- $\alpha$ therapy for one year; others underwent topical or phototherapy to determine the association between changes in skin disease severity and aortic vascular inflammation.	1. Aortic vascular inflammation measured as TTB ratio by $^{18}\text{F}$ -FDG PET/CT 2. PASI-75	1. In 17 patients on anti-TNF- $\alpha$ therapy, 67% reduction in psoriasis severity (P=0.002) and 6% reduction in vascular inflammation (P=0.04) 2. Entire cohort had 33% reduction in psoriasis severity (p<0.001) and 6% reduction in vascular inflammation	Uniform therapy throughout entire cohort was lacking. Cardiovascular events as a result of anti-TNF- $\alpha$ therapy were not examined.
Jokai et al. (2013) [2] Country: Hungary	6-month pilot study on 16 patients with severe plaque-type psoriasis treated with anti-TNF- $\alpha$ therapy (3 on etanercept, 7 on infliximab, and 6 on adalimumab) to determine if long-term anti-TNF- $\alpha$ therapy decreases vascular IMT.	1. Carotid and brachial artery IMT measured by high-resolution, B-mode ultrasonography	1. Carotid and brachial IMT values significantly decreased in group without initially visible atherosclerosis (n=13, P=0.0002) after anti-TNF- $\alpha$ therapy 2. Group with initial atherosclerosis did not show any significant change in IMT (n=3) after anti-TNF- $\alpha$ therapy	The clinical effect of improvement in carotid and brachial IMT after anti-TNF- $\alpha$ therapy was not studied and no conclusions in that regard could be deduced.

Table 1 (continued). *Studies examined, and a summary of their results [1-5].*

<p>Naik et al. (2015) [3] Country: USA</p>	<p>Prospective observation of 60 adults with psoriasis to understand whether psoriasis severity is associated with aortic vascular inflammation; 20 controls.</p>	<ol style="list-style-type: none"> <li>1. Aortic vascular inflammation measured as average TTB ratio by <sup>18</sup>F-FDG PET/CT as related to PASI score</li> <li>2. Transcriptome analysis of inflammatory biomarkers in psoriasis</li> </ol>	<ol style="list-style-type: none"> <li>1. There is a positive correlation between PASI score and aortic vascular TTB ratio (P=0.001)</li> <li>2. Psoriasis severity is associated with aortic vascular inflammation independent of CV risk factors (P=0.002 after adjusting for age and sex, and P=0.001 after adjusting for FRS)</li> <li>3. Transcriptome analysis expressed cytokines and chemokines upregulated in psoriasis and atherosclerosis (TNF-<math>\alpha</math>, IL-6, and IL-17), although without statistical significance</li> </ol>	<p>Study is limited by cross-sectional design and inability to convey clinical causality between extent of PASI and aortic vascular inflammation. Furthermore, correlation between reduction in aortic vascular inflammation and clinical cardiovascular adverse events was lacking.</p>
<p>Kim et al. (2018) [4] Country: South Korea</p>	<p>Prospective feasibility study to determine if ustekinumab (anti-interleukin 12/23 monoclonal antibody) reduces aortic vascular and systemic inflammation associated with metabolic syndrome and CVD in 10 patients with severe psoriasis; 47 controls.</p>	<ol style="list-style-type: none"> <li>1. Aortic vascular inflammation measured as TTB ratio by <sup>18</sup>F-FDG PET/CT after PASI-75 achieved from drug use at 5 different points along the aorta</li> <li>2. Hepatic and splenic inflammation measured by <sup>18</sup>F-FDG uptake on <sup>18</sup>F-FDG PET/CT</li> </ol>	<ol style="list-style-type: none"> <li>1. After 5 months of ustekinumab therapy in 10 severe psoriasis patients, there was a decrease in aortic vascular (p&lt;0.05), hepatic and splenic inflammation</li> </ol>	<p>No outcome data obtained regarding cardiovascular events; limited Korean population</p>
<p>Hjuler et al. (2016) [5] Country: Denmark</p>	<p>Controlled, observer-blinded observation study investigating association between psoriasis biologic therapy (adalimumab, etanercept, infliximab, and ustekinumab) in 28 patients with moderate-to-severe psoriasis (PASI at least 10 and no history of CAD, major uncontrolled CV risk factors, and no prior CV events or coronary artery revascularization) with changes in CAD progression; 28 controls.</p>	<ol style="list-style-type: none"> <li>1. Non-contrast CAC CT</li> <li>2. Contrast-enhanced coronary CT angiography</li> <li>3. PASI score</li> <li>4. Changes in CAC, number of coronary plaques, severity of luminal narrowing, composition and vessel wall volume</li> </ol>	<ol style="list-style-type: none"> <li>1. CAC score remained stable in treated group (P=0.15); worsened in control group (P=0.02)</li> <li>2. Number of segments with luminal abnormalities unchanged in both groups</li> <li>3. Severity of luminal narrowing in diseased segments unchanged in treated group (P=0.39); worsened in controls (P=0.02)</li> <li>4. Vessel wall volume index remained unchanged in treated group (P=0.91); worsened in control group without statistical significance (P=0.06)</li> </ol>	<p>Findings cannot be applied to patients with moderate-to-severe psoriasis with known initial CAD. Cannot deduce the risk reduction of CV events in treated group despite decreased CAD progression based on various measurement parameters.</p>

Table 1 (continued). *Studies examined, and a summary of their results [1-5].*

Table 1 Key: PASI (Psoriasis Area Severity Index); PASI-75 (PASI score at greater than 75% improvement in psoriasis severity); TTB (target-to-background); FRS (Framingham Score); CV (cardiovascular); CAD (coronary artery disease); <sup>18</sup>F-FDG PET/CT (<sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography); <sup>18</sup>F-FDG (<sup>18</sup>F-fluorodeoxyglucose); IMT (intima-media thickness); IL-6 (interleukin-6); IL-17 (interleukin-17); CAC (coronary artery calcium).

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